ORIGINAL ARTICLE

Efficacy, Immunogenicity, and Safety of Modified mRNA Influenza Vaccine

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ABSTRACT

BACKGROUND

Influenza remains a major health burden despite the use of licensed vaccines. Nucleoside-modified messenger RNA (modRNA) influenza vaccines have shown promising immunogenicity against influenza and an acceptable safety profile in a phase 1–2 trial.

METHODS

In this phase 3 trial, we randomly assigned healthy adults between the ages of 18 and 64 years to receive either a quadrivalent modRNA influenza vaccine (modRNA group) or a licensed inactivated quadrivalent influenza vaccine (control group) during the 2022–2023 influenza season in the United States, South Africa, and the Philippines. The primary end point was relative efficacy, defined by the reduction in the percentage of participants with laboratory-confirmed influenza associated with influenza-like illness at least 14 days after vaccination with the modRNA vaccine, as compared with the control vaccine, and analyzed for noninferiority and superiority. Immunogenicity was evaluated by means of a hemagglutination inhibition (HAI) assay. We assessed reactogenicity within 7 days after vaccination, adverse events through 1 month, and serious adverse events through 6 months. We assessed vaccine efficacy, immunogenicity, and safety in the modRNA group.

RESULTS

A total of 18,476 participants underwent randomization: 9225 were assigned to receive the modRNA vaccine and 9251 to receive the control vaccine. The relative efficacy of the modRNA vaccine as compared with the control vaccine against influenza-like illness was 34.5% (95% confidence interval [CI], 7.4 to 53.9) on the basis of 57 cases in the modRNA group and 87 cases in the control group, a finding that met the criteria for both noninferiority and superiority. Cases of influenza-like illness were caused by A/H3N2 and A/H1N1 strains but almost no B strains. The noninferiority of the antibody response on HAI assay was shown for influenza A strains but not for B strains. Primarily mild or moderate reactogenicity was observed in both vaccine groups but was reported more frequently in the modRNA group (overall local reactions, 70.1% vs. 43.1%; overall systemic events, 65.8% vs. 48.7%). Fever occurred in 5.6% of the participants in the modRNA group and in 1.7% of those in the control group. Adverse event profiles were similar in the two groups.

CONCLUSIONS

The modRNA vaccine had statistically superior efficacy over the control vaccine, with greater immune responses to A/H3N2 and A/H1N1 strains, but was associated with more reactogenicity events. (Funded by Pfizer; C4781004 ClinicalTrials.gov number, NCT05540522.)

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Influenza continues to cause widespread disease across age groups.[1] During the 2022–2023 influenza season in the United States, influenza led to an estimated 130,000 hospitalizations and more than 5500 deaths among adults between the ages of 18 and 64 years.[1] In that same season, vaccination prevented an estimated 2.8 million influenza-related illnesses, 22,000 hospitalizations, and more than 1000 deaths in this age group.[2] However, overall vaccine effectiveness against influenza is suboptimal, with a range of 10 to 60% from 2004 through 2023.[3] The match between vaccine antigens and circulating influenza viruses, which change rapidly owing to viral genetic instability, can have an effect on efficacy.[4,5] Annual vaccine production is required to better match circulating strains and because strain-specific immunity wanes over time.[6]

Nucleoside-modified messenger RNA (modRNA)–based vaccines have become integral to vaccine development. During the coronavirus disease 2019 (Covid-19) pandemic, licensed lipid nanoparticle–encapsulated modRNA vaccines encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein were highly effective.[7,8] ModRNA-based vaccines, in which some nucleosides are replaced by naturally occurring modified nucleosides, decrease innate immune activation and increase translation.[9] The modRNA platform offers unique advantages over traditional egg-based vaccines, including larger-scale production, direct matching of the vaccine to the targeted influenza strain, potential for shorter manufacturing timelines between strain selection and vaccine production, and no risk of egg-adaptive mutations, which can decrease effectiveness.[10-13]

A quadrivalent modRNA influenza vaccine candidate has shown promising immunogenicity and an acceptable safety profile in a phase 1–2 investigation.[14] We conducted a phase 3 efficacy trial — A Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Modified RNA Vaccine against Influenza (Pfizer C4781004 trial) — to determine the relative efficacy of the modRNA vaccine as compared with a standard quadrivalent vaccine against influenza.

Methods

Participants and Trial Design

This randomized, blinded trial enrolled participants at 242 sites in the United States, 5 sites in South Africa, and 1 site in the Philippines during the 2022–2023 influenza season. The trial design called for the evaluation of the efficacy, safety, and immunogenicity of the modRNA vaccine encoding hemagglutinins of four influenza strains (two strains each of influenza A and B), as recommended by the World Health Organization (WHO) for that season (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

We assigned healthy or medically stable participants between the ages of 18 and 64 years in a 1:1 ratio to receive an intramuscular injection of the modRNA vaccine (at a dose of 30 μg) or an inactivated comparator (FLUZONE [Sanofi Pasteur]) as a control vaccine. Participants could not have received any influenza vaccine within 6 months before the trial. Details regarding eligibility criteria and ethical trial conduct are provided in the Supplementary Appendix. The trial was approved by the institutional review board at each site, and all the participants provided written informed consent.

Oversight

The trial was designed and conducted by the sponsor, Pfizer. Representatives of the sponsor performed the collection, analysis, and interpretation of the data. The modRNA vaccine was provided by the sponsor, and the control vaccine was purchased from a wholesale supplier. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org).

Efficacy

Our primary objective was to show the noninferiority and superiority of the modRNA vaccine to the control vaccine against laboratory-confirmed influenza associated with influenza-like illness, according to the protocol definition. Relative vaccine efficacy was defined as the relative reduction in the percentage of participants with a first episode of influenza-like illness at least 14 days after vaccination with the modRNA vaccine as compared with the control vaccine.

Secondary efficacy end points were the first episode of laboratory-confirmed influenza-like illness caused by all antigenically matched strains, by unmatched strains, and by each matched strain; culture-confirmed influenza-associated illness (any strain); laboratory-confirmed influenza as defined by the WHO and the Centers for

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Disease Control and Prevention (CDC; modified definition); and all local or central laboratory-confirmed cases of influenza-like illness. An exploratory end point was the relative vaccine efficacy against a first episode of influenza-like illness at least 7 days after vaccination. Case definitions are provided in Table S2; details regarding disease surveillance and viral testing are provided in the Supplementary Appendix.

IMMUNOGENICITY

We assessed immunogenicity in approximately 4000 participants (immunogenicity subgroup). Blood was collected before vaccination and at 4 weeks and 6 months after vaccination. Optional blood samples were also collected from approximately 125 participants in the immunogenicity subgroup to assess cell-mediated immune responses (peripheral-blood mononuclear cell [PBMC] subgroup). A secondary immunogenicity end point was to show the noninferiority of the immune response to the modRNA vaccine as compared with the control vaccine.

Immunogenicity end points included geometric mean ratios of titers on the hemagglutination inhibition (HAI) assay and the between-group difference in the percentage of participants with seroconversion for each strain 4 weeks after vaccination. HAI assays were performed with egg-derived and cell-derived influenza viruses corresponding to egg-based and cell-based assays for WHO-recommended strains (two strains each of influenza A and B) for the respective vaccines during the 2022–2023 influenza season in the Northern Hemisphere (Table S1).

An additional secondary immunogenicity end point was the immune response elicited by the modRNA vaccine 4 weeks after vaccination. The persistence of immune response 6 months after vaccination was examined in an exploratory analysis. Other end points included HAI geometric mean titers (GMTs) at each time point, the geometric mean factor increase (i.e., the geometric mean of the ratios of postvaccination titers to prevaccination titers) in HAI at each time point, and the percentages of participants with HAI seroconversion for each strain at each time point and with HAI titers of at least 1:40 for each strain prevaccination and 4 weeks postvaccination.

Exploratory immunogenicity end points included the between-group difference in cell-mediated immune response (the geometric mean frequencies of hemagglutinin-specific CD4+ and CD8+ T cells at each PBMC collection time point) and the geometric mean factor increase for hemagglutinin-specific CD4+ and CD8+ T-cell frequencies from prevaccination to each postvaccination PBMC collection time point, as determined by means of intracellular cytokine staining assay.

SAFETY

The primary safety objective was to define the safety and side-effect profile for the modRNA vaccine. Safety assessments included solicited local reactions and systemic events (reactogenicity) within 7 days after vaccination (as documented by a subgroup of participants in an electronic diary), adverse events through 4 weeks, and serious adverse events through 6 months. Prespecified events of clinical importance — myocarditis and pericarditis, anaphylactic reactions, and autoimmune conditions — were analyzed through 6 months after vaccination. Details regarding the monitoring for myocarditis and pericarditis are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

With the expected enrollment of approximately 17,600 participants, we determined that the first 152 cases of laboratory-confirmed influenza, according to the protocol definition, would provide the trial with approximately 80% power to meet the primary efficacy end point of showing the noninferiority of the modRNA vaccine to the control vaccine with a one-sided type I error of 2.5%; with the same end point, 212 cases of influenza-like illness would provide approximately 90% power. (Details regarding the sample-size determination are provided in the Supplementary Appendix.)

Hypothesis testing for the efficacy and immunogenicity end points was performed in a hierarchical manner, with two hypotheses (noninferiority and superiority) for primary efficacy and eight hypotheses for secondary immunogenicity end points (two hypotheses for each strain) (Table S3).

Efficacy end-point analyses were performed on evaluable efficacy data in the modified intention-to-treat population. The evaluable efficacy population — the primary population for hypothesis testing related to primary efficacy objectives — included all the participants who had been vaccinated in their assigned group and who had no important protocol deviations or influenza-like illness within 14 days after vaccination

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(Table S4). Primary analyses of efficacy objectives were based on 144 cases of influenza-like illness that accrued before the data-cutoff date (March 17, 2023). Analyses were also conducted through the influenza end-of-season date (May 1, 2023), as determined by the sponsor's review of CDC epidemiologic trends.

For primary efficacy objectives, the relative vaccine efficacy was estimated along with two-sided 95% confidence intervals. The relative vaccine efficacy was calculated as 1−(number of first-episode influenza-like illnesses/total number in the modRNA group÷number of first-episode influenza-like illnesses/total number in the control group). Efficacy analyses used conditional-exact tests based on binomial distribution of numbers of first-episode cases of influenza-like illness in the modRNA group, given the total number of first-episode cases in both groups. Primary efficacy objectives were evaluated sequentially after the accrual of at least 130 first episodes of evaluable cases of influenza-like illness caused by any strain. P values were not calculated for relative vaccine efficacy.

Noninferiority efficacy testing of the modRNA vaccine as compared with the control vaccine against influenza-like illness was followed by superiority testing. Noninferiority or superiority was declared if the lower boundary of the two-sided 95% confidence interval for relative vaccine efficacy was more than −10 percentage points for noninferiority and more than 0 percentage points for superiority. For secondary and exploratory efficacy objectives, relative vaccine efficacy and two-sided 95% confidence intervals were estimated.

Immunogenicity analyses were performed in populations of participants with evaluable immunogenicity data. We calculated GMTs, HAI geometric mean factor increases, and geometric mean ratios by exponentiation of means, mean factor increases (earlier to later values), and mean ratios of the unadjusted HAI titers in the two groups, respectively. The 95% confidence interval for the population mean was calculated by means of Student's t-distribution. Seroconversion was defined as an HAI titer of less than 1:10 before vaccination and a titer of at least 1:40 after vaccination or an HAI titer of at least 1:10 before vaccination and a factor increase of at least four after vaccination.

Because the protocol did not include a provision for multiplicity correction in the assessment of secondary or other end points (aside from secondary immunogenicity end points for noninferiority), the results are reported as point estimates and 95% confidence intervals. The widths of these intervals have not been adjusted for multiplicity, so intervals should not be used to infer definitive effectiveness for secondary end points that are not related to the immunogenicity noninferiority objective.

If both primary efficacy objectives were met in the evaluable efficacy population, hypothesis testing for the noninferiority of the immune response was performed in a hierarchical manner according to strain (A/H3N2, A/H1N1, B/Yamagata, and B/Victoria sequentially) for HAI assay results based on egg-derived virus, followed by testing of each strain for HAI assay results based on cell-derived virus. If the lower boundary of the two-sided 95% confidence interval for between-group comparisons met two criteria — a value of more than 0.67 (a factor margin of 1.5) for the efficacy of the modRNA vaccine over the control vaccine and a value of more than −10 percentage points for the difference between vaccines in the percentage of participants with seroconversion (modRNA minus control) — noninferiority was declared for a strain. Data regarding PBMC analyses are presented descriptively as geometric mean percentages, and the geometric mean factor increase is summarized for cell-based hemagglutinin–specific CD4+ and CD8+ T cells from prevaccination to each postvaccination time point.

Safety analyses were descriptive. Reactogenicity events were assessed in the reactogenicity electronic-diary subgroup and other safety events in the safety populations.

RESULTS

PARTICIPANTS

From October 24, 2022, to January 30, 2023, a total of 18,476 participants underwent randomization (with 9225 assigned to the modRNA group and 9251 assigned to the control group). Of these participants, 9191 received the modRNA vaccine and 9197 received the control vaccine. A total of 92.9% of the participants in the two groups completed the 6-month follow-up (Fig. S1). The demographic characteristics of the participants

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were similar in the two trial groups (Table S5) and were representative of the expected target population (Table S6). The mean age of the participants was 43 years, 41.9% were men, and 73.6% were White; 25.1% had at least one risk factor for severe influenza.

EFFICACY

At the data-cutoff date for the primary efficacy analyses, 57 cases of influenza-like illness had accrued in the modRNA group and 87 cases in the control group (Fig. 1A). For the primary efficacy end point, the relative efficacy of the modRNA vaccine as compared with the control vaccine against a first episode of influenza-like illness occurring at least 14 days after vaccination was 34.5% (95% confidence interval [CI], 7.4 to 53.9), a finding that met the criteria for both noninferiority and superiority (Fig. 1B). The relative vaccine efficacy in the modified intention-to-treat efficacy population was 33.6% (95% CI, 12.5 to 49.8) (Fig. S2). In the end-of-season analysis in the evaluable efficacy population, the relative vaccine efficacy was 28.7% (95% CI, 0.1 to 49.4) (Fig. S3).

For secondary efficacy, the relative vaccine efficacy point estimates for antigenically matched strains are shown in Figure 2 for the primary

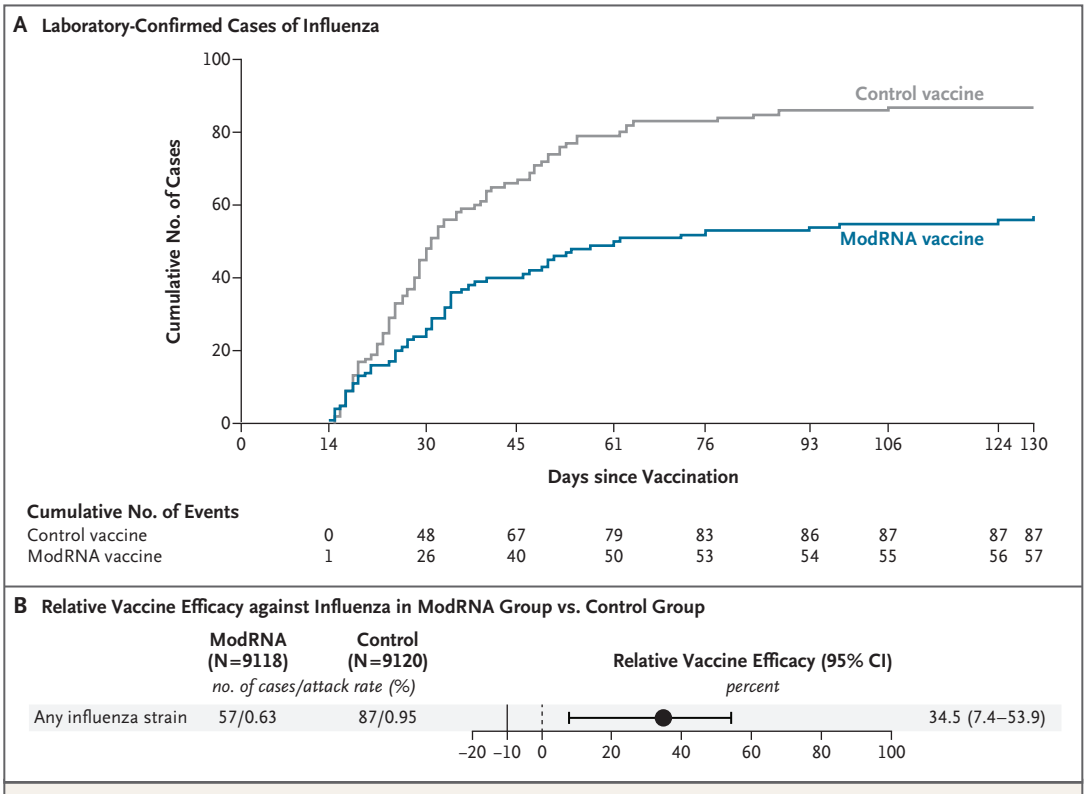
A Laboratory-Confirmed Cases of Influenza
Cumulative No. of Cases
100
80
60
40
20
0
Control vaccine
ModRNA vaccine
0 14 30 45 61 76 93 106 124 130
Days since Vaccination
Cumulative No. of Events
Control vaccine 0 48 67 79 83 86 87 87 87
ModRNA vaccine 1 26 40 50 53 54 55 56 57
B Relative Vaccine Efficacy against Influenza in ModRNA Group vs. Control Group
ModRNA (N=9118)
Control (N=9120)
no. of cases/attack rate (%)
Relative Vaccine Efficacy (95% CI)
percent
Any influenza strain 57/0.63 87/0.95 34.5 (7.4–53.9)
–20 –10 0 20 40 60 80 100

Figure 1. Relative Vaccine Efficacy (Primary End Point).

Panel A shows the cumulative number of laboratory-confirmed cases of influenza-like illness among participants who received the quadrivalent nucleoside-modified messenger RNA (modRNA) influenza vaccine (modRNA group) or a licensed inactivated quadrivalent influenza vaccine (control group). Panel B shows the relative vaccine efficacy against the first episode of influenza-like illness caused by any strain in the modRNA group as compared with the control group. Data in both panels are for the evaluable efficacy population and include influenza-like illness with symptom onset starting at least 14 days after vaccination through the surveillance data-cutoff date (March 17, 2023). The attack rate was calculated as the total number of cases divided by the number of participants at risk times 100. In Panel B, noninferiority of the modRNA vaccine was shown if the lower boundary of the confidence interval for the relative vaccine efficacy was greater than –10 percentage points (indicated by a solid vertical black line), and superiority was shown if the lower boundary was greater than 0 percentage points (indicated by a dashed vertical black line).

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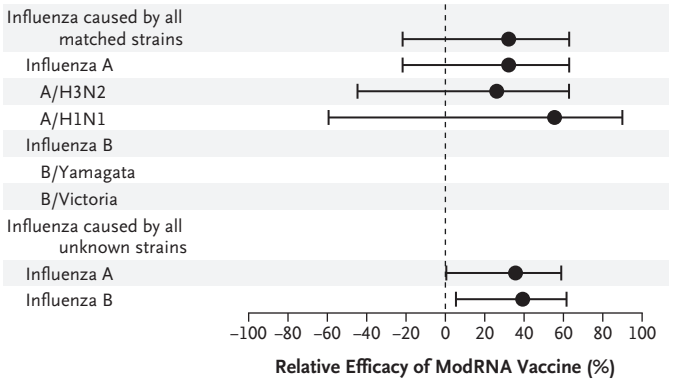

Figure 2. Relative Vaccine Efficacy, According to Influenza Strain.

Shown are data for the relative efficacy of the modRNA vaccine as compared with the licensed quadrivalent influenza (control) vaccine against a first episode of influenza-like illness with symptom onset at least 14 days after vaccination, according to the influenza strain (a secondary efficacy end point). Matched strains were culture-confirmed influenza strains that were antigenically similar to the vaccine strain (difference in hemagglutination inhibition [HAI] titers to a reference virus strain by a factor of 4 or less). Confidence intervals were not adjusted for multiplicity and should not be used to infer effects.

analysis, in Figure S4 for the end-of-season analysis of unmatched strains, and in Table S7 for different clinical definitions and methods of laboratory confirmation of influenza. No matched cases of influenza B virus were reported; two cases of unknown strains of influenza B were reported in the modRNA group. The observed relative vaccine efficacy against influenza-like illness at least 7 days after vaccination (35.8%) was similar to the efficacy observed for the primary end point evaluated at least 14 days after vaccination (Fig. S5).

IMMUNOGENICITY

Observed geometric mean ratios on the HAI assay (modRNA-to-control) for A/H3N2 and A/H1N1 strains at 4 weeks postvaccination met the prespecified noninferiority criterion for modRNA (lower boundary of the two-sided 95% confidence interval, >0.67) (Fig. 3A). Noninferiority was not shown for the B/Yamagata and B/Victoria strains. The difference (modRNA minus control) in percentages of participants with seroconversion for A/H3N2 and A/H1N1 strains from prevaccination to 4 weeks postvaccination met the prespecified noninferiority criterion for modRNA (lower boundary of the two-sided 95% confidence interval of more than –10 percentage points) (Fig. 3B). Again, noninferiority was not shown for the B/Yamagata and B/Victoria strains. Of the four strains of influenza A that were tested, the lower boundary of the 95% confidence interval for seroconversion was more than 40% for two strains (A/H3N2 and A/H1N1) in the modRNA group and for three strains (A/H3N2, A/H1N1, and B/Victoria) in the control group.

Because noninferiority was not shown for geometric mean ratios on the HAI assay or seroconversion for all four vaccine strains on egg-derived virus HAI assays, prespecified hierarchical noninferiority testing was not continued; therefore, cell-derived virus results on HAI assays are descriptive. Cell-derived assay results were consistent with those of egg-derived assays and are presented in Figures S6 through S9.

In the evaluable immunogenicity population, GMTs on the HAI assay increased from prevaccination to 4 weeks postvaccination in the two trial groups (Fig. S10). Postvaccination GMTs were higher for A strains than for B strains and were higher with the modRNA vaccine than with the control vaccine for A strains and lower for B strains across the trial groups.

Before vaccination, more than 50% of the participants in the evaluable immunogenicity population had preexisting HAI titers of at least 1:40 for A/H3N2, A/H1N1, and B/Yamagata strains, with percentages balanced between the modRNA group and the control group. At 4 weeks postvaccination, the percentages of participants who had HAI titers of at least 1:40 rose for all strains in the two trial groups. The lower boundary of the 95% confidence interval for the percentage of participants who had HAI titers of at least 1:40 was more than 70% for three of the four strains (A/H3N2, A/H1N1, and B/Yamagata) in the two trial groups, which indicated that both vaccines elicited seroprotective responses against influenza in the majority of participants.

The geometric mean factor increase in the CD4+ and CD8+ T-cell expression of interferon-γ and frequencies of response were higher in the modRNA group than in the control group for all strains 1 week after vaccination, particularly for CD8+ T-cell expression with the two B strains (Fig. 4). This pattern was also maintained at 4 weeks and 6 months postvaccination (Fig. S11).

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SAFETY

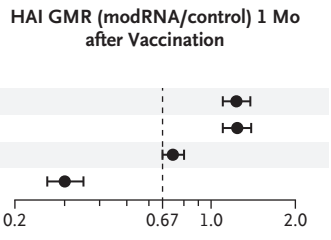
Among 6127 participants in the reactogenicity electronic-diary subgroup, recipients of the modRNA vaccine reported more local reactions and systemic events than control recipients (70.1% vs. 43.1% for local reactions and 65.8% vs. 48.7% for systemic events) (Fig. 5 and Table S8). Reactogenicity events were generally mild to moderate, with no clinically meaningful differences between groups in severe events. Pain was the most common local reaction, and fatigue and headache were the most common systemic events. Fever (≤40.0°C) occurred in 5.6% of the participants in the modRNA group and in 1.7% of those in the control group. The median onset of local reactions was 2 days after vaccination in the modRNA group and 1 to 2 days in the control group; the duration of local reactions was also 2 days and 1 to 2 days, respectively. The median onset of systemic events was 2 to 3 days in the modRNA group and 2 to 4 days in the control group; the duration of systemic events was 1 to 2 days after each vaccine.

Among the 18,388 participants in the safety data set, at the time of the safety data cutoff (September 29, 2023), adverse events had been reported through 4 weeks after vaccination by 6.7% of the participants in the modRNA group and by 4.9% of those in the control group (Fig. S12). Adverse events that were considered by the investigator to be related to the vaccine were reported in 3.3% of modRNA recipients and in 1.4% of control recipients (Table S9). The higher frequency of adverse events with modRNA was driven mostly by reactogenicity events occurring within 7 days after vaccination that were reported by participants who were not in the reactogenicity electronic-diary subgroup.

Frequencies of severe and life-threatening adverse events, serious adverse events, and adverse events leading to withdrawal from the trial were low and similar in the two trial groups

A Egg-Derived Viral Titers and Ratios on HAI Assay

	No. of Participants		HAI GMT (95% CI)	
	ModRNA	Control	ModRNA	Control
A/Darwin/9/2021 (A/H3N2)	738	746	222.3 (206.0–240.0)	180.4 (166.6–195.4)
A/Victoria/2570/2019 (A/H1N1)	738	746	397.7 (367.8–430.0)	321.7 (294.6–351.2)
B/Phuket/3073/2013 (B/Yamagata)	736	743	84.5 (79.4–90.0)	115.9 (108.5–123.8)
B/Austria/1359417/2021 (B/Victoria)	734	736	21.3 (19.3–23.6)	70.6 (63.6–78.4)



B Seroresponse Results

	No. of Participants		Seroresponse (95% CI)	
	ModRNA	Control	ModRNA	Control
			percent	
A/Darwin/9/2021 (A/H3N2)	735	746	64.2 (60.6–67.7)	52.8 (49.2–56.4)
A/Victoria/2570/2019 (A/H1N1)	735	743	66.1 (62.6–69.5)	52.5 (48.8–56.1)
B/Phuket/3073/2013 (B/Yamagata)	736	743	13.9 (11.4–16.6)	29.2 (26.0–32.6)
B/Austria/1359417/2021 (B/Victoria)	731	733	11.4 (9.1–13.9)	51.8 (48.2–55.5)

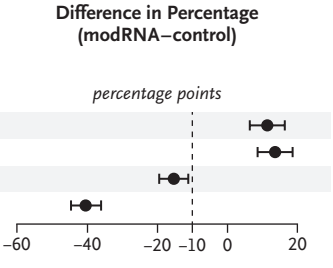


Figure 3. HAI Titer and Seroresponse 4 Weeks after Vaccination, According to Strain.

Shown are HAI geometric mean titers (Panel A) and seroresponse (Panel B) among patients in the evaluable immunogenicity population in the modRNA group and the control group, according to viral strain. The lower limit of quantitation (LLOQ) for each strain-specific HAI titer was 10. Assay results below the LLOQ were set at 0.5×LLOQ for this analysis. The upper limit of quantitation (ULOQ) for A/H3N2, A/H1N1, B/Yamagata, and B/Victoria HAI titers was 5120, 2560, 5120, and 2560, respectively. Assay results above the ULOQ were set to ULOQ+1 for analysis. In Panel A, the geometric mean ratio (GMR) was estimated as the ratio of the HAI titer in the modRNA group to that in the control group. In Panel B, a seroresponse was defined as a titer of less than 1:10 before vaccination and of 1:40 or more at 4 weeks after vaccination or a titer of 1:10 or more before vaccination with a factor increase of four at 4 weeks after vaccination. The difference in seroresponse is expressed as a percentage. In both panels, I bars represent 95% confidence intervals, and the dotted lines represent noninferiority criteria.

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(Tables S10 and S11). One recipient of the modRNA vaccine had serious adverse events that were considered by the investigator to be vaccine-related (a grade 3 vaccination-site reaction and a grade 4 anaphylactic reaction, an event that did not meet the standard clinical criteria for anaphylaxis). No other events of anaphylaxis were reported.

Through 6 months after vaccination, 16 participants had an adverse event with a fatal outcome (7 in the modRNA group and 9 in the control group); none of these events were considered by the investigator to be vaccine-related (Table S12). No deaths were reported during the week after vaccination; 2 deaths (both in the control group) were reported from day 8 through week 4 after vaccination. No participant had confirmed myocarditis or pericarditis. Immune or autoimmune disorders had similar frequencies of diagnosis in the two groups.

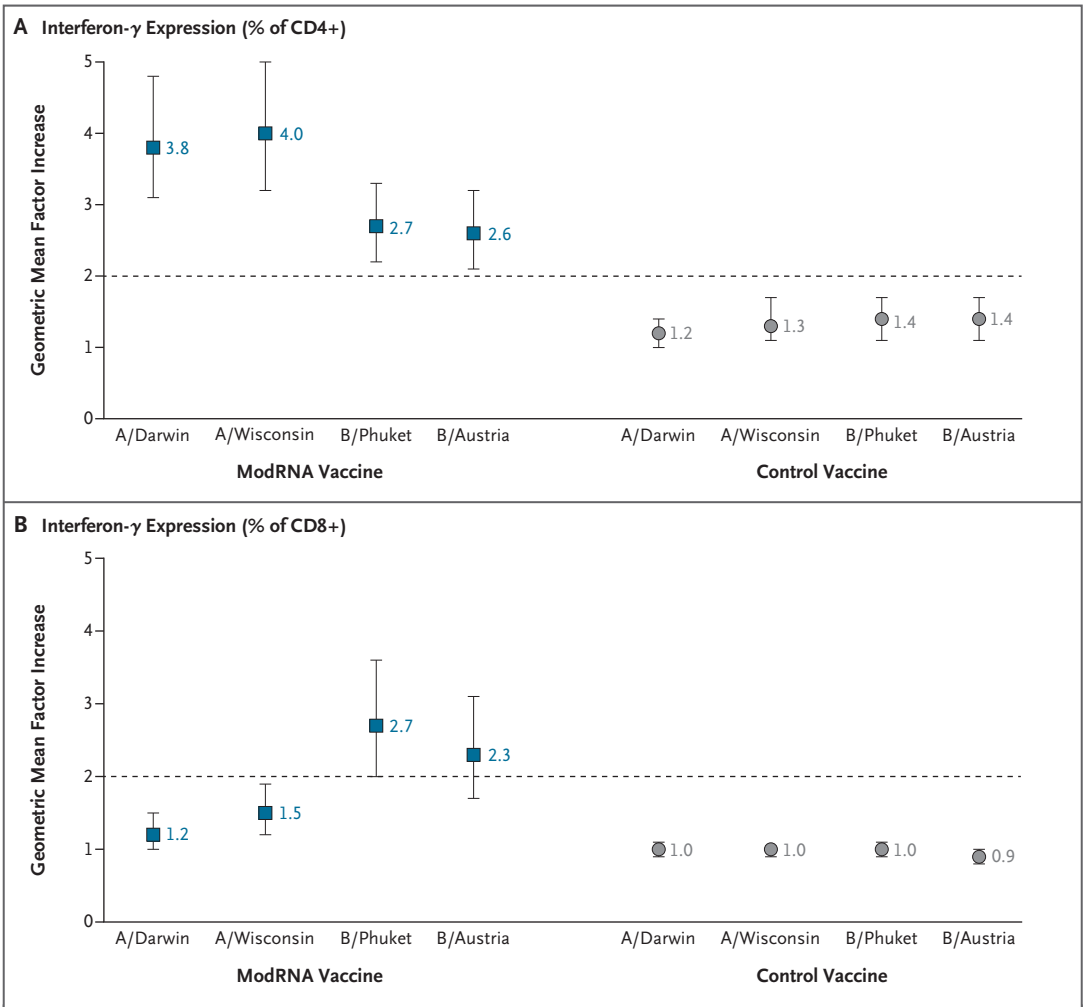

Figure 4. T-Cell Expression of Interferon-γ at 1 Week after Vaccination.

Shown are results in the participants who underwent evaluation of peripheral-blood mononuclear cells for T-cell expression of interferon-γ, according to the percentage of CD4+ and CD8+ cells. The response is reported as the geometric mean factor increase in the T-cell percentage. The LLOQ value for the intracellular cytokine staining assay was 0.00260 for CD4+ cells and 0.01636 for CD8+ cells. Influenza strains that were evaluated included A/Darwin/6/2021 (A/H3N2), A/Wisconsin/588/2019 (A/H1N1), B/Phuket/3073/2013 (B/Yamagata), and B/Austria/1359417/2021 (B/Victoria). Confidence intervals (represented by I bars) were not adjusted for multiplicity and should not be used to infer effects.

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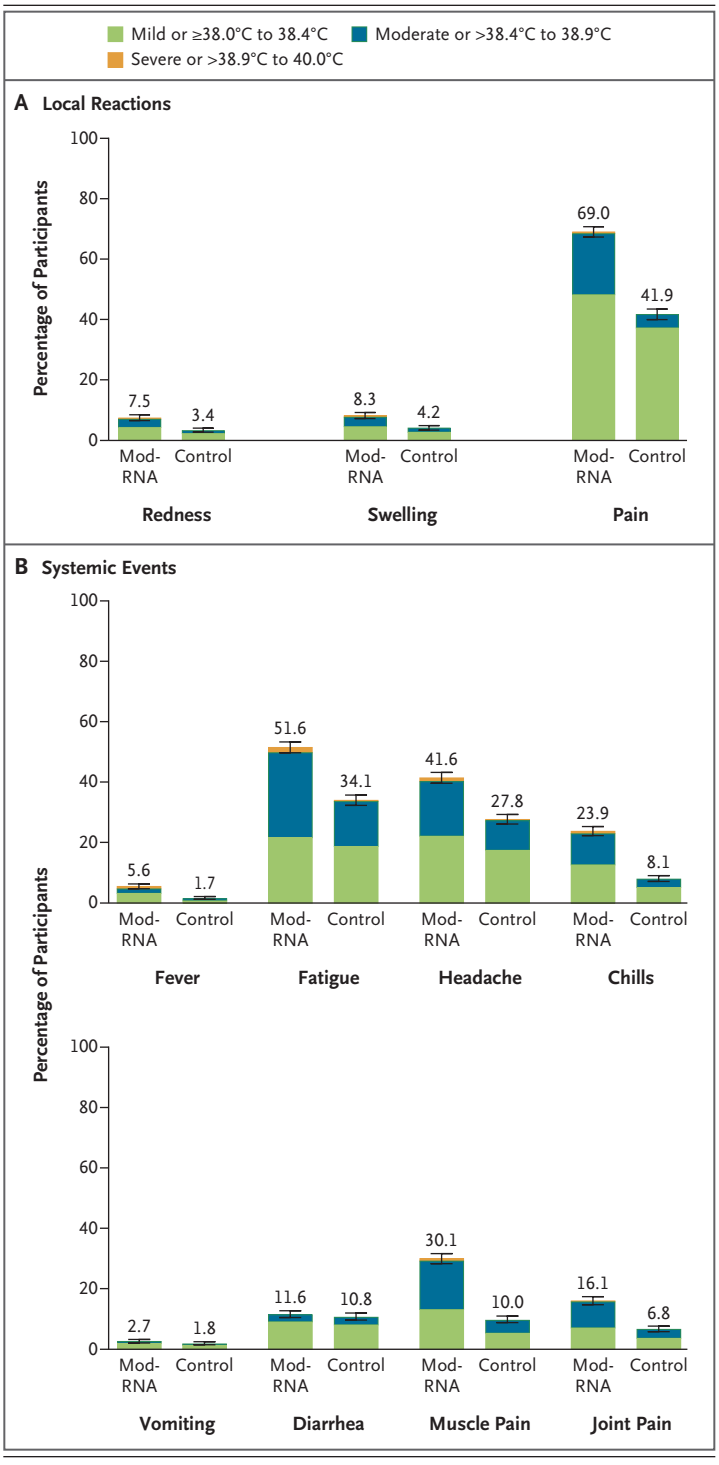
Figure 5. Local Reactions and Systemic Events within 7 Days after Injection.

Shown are local reactions (Panel A) and systemic events (Panel B) in 3060 recipients of the modRNA vaccine and in 3067 recipients of the control vaccine. Data are for the participants who kept an electronic diary of reactogenicity events. The demographic characteristics of this population are shown in Table S8. Severity grading scales are summarized in Table S13. The numbers above the bars show the percentage of participants in each group with the specified local reaction (mild, moderate, or severe) or systemic event (temperature range). In the modRNA group, severe redness was reported by 11 participants (0.4%) and severe swelling by 14 participants (0.5%); severe injection-site pain was reported by 17 participants (0.6%) in the modRNA group and 1 participant (<0.1%) in the control group. Fever in a range of 38.9°C to 40.0°C was reported by 24 participants (0.8%) in the modRNA group and 7 participants (0.2%) in the control group; severe fatigue by 51 participants (1.7%) and 13 participants (0.4%), respectively; severe headache by 38 participants (1.2%) and 13 participants (0.4%), respectively; severe chills by 29 participants (0.9%) and 3 participants (<0.1%), respectively; severe diarrhea by 4 participants (0.1%) and 4 participants (0.1%), respectively; severe muscle pain by 25 participants (0.8%) and 7 participants (0.2%), respectively; and severe joint pain by 9 participants (0.3%) and 3 participants (<0.1%), respectively. One participant who received the modRNA vaccine reported having grade 4 diarrhea.



DISCUSSION

In this trial, we evaluated the relative efficacy of a modRNA vaccine in preventing influenza as compared with a licensed influenza control vaccine. The relative vaccine efficacy in participants ranging in age from 18 to 64 years was shown in a Northern Hemisphere influenza season dominated by the distribution of the A/H3N2 strain, followed to a lesser extent by the A/H1N1 strain.[15] The modRNA vaccine showed efficacy overall.

During the 2022–2023 influenza season, U.S.-licensed influenza vaccines had a vaccine effectiveness of approximately 44 to 54% in participants who were 64 years of age or younger.[16,17] Concurrent evaluation of the U.S.-licensed control vaccine that was included in our trial within the same season allowed for comparisons with the modRNA vaccine. In the end-of-season analysis, the 28.7% relative efficacy of the modRNA vaccine as compared with the control vaccine suggests that the efficacy of the modRNA vaccine ranged from 60 to 67%.

We evaluated immune responses using HAI assays for the serologic response and intracellular cytokine staining for the cell-mediated immune response to each vaccine. Antibody responses with the modRNA vaccine were higher

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than those with the control vaccine for A strains and were similar to or lower than those with the control vaccine for B strains at 4 weeks and 6 months after vaccination. The results of testing for cell-mediated immune response showed CD4+ and CD8+ influenza antigen-specific activation from 1 week through 6 months after receipt of the modRNA vaccine. T-cell expression of interferon-γ with the modRNA vaccine was generally higher for all four strains at all time points tested, with detectable cell-mediated immune responses at 6 months for all strains.

As compared with the control vaccine, increased HAI antibody responses with the modRNA vaccine corresponded to higher relative vaccine efficacy against matched A strains, regardless of HAI assay type. Only two B-strain cases were observed during this trial, both with unknown strains, a finding that was consistent with contemporaneous surveillance data. During the reported U.S. influenza season, 95.4% of cases were caused by influenza A, with A/H3N2 accounting for 57.1% of all positive specimens; A/H1N1 (24.1%) and B/Victoria (3.8%) specimens were also reported.[18] The underperformance of HAI assays in detecting B-strain responses has been described previously, which suggests an uncertainty regarding the ability of this assay to predict protection against influenza B.[19] Our trial did not improve our understanding of protection against influenza B illness with either vaccine.

Reactogenicity events were reported more frequently with the modRNA vacine than with the control vaccine. However, most of these events were mild or moderate and generally transient, with no clinically meaningful differences in severe events between groups. The modRNA safety profile was generally similar to that of the control vaccine, with no new safety concerns identified. Adverse events generally reflected age-appropriate illnesses, infections, and conditions expected in this population. The frequencies of serious adverse events through 6 months were similar (approximately 1.0%) in the two groups.

Limitations of the trial include the use of relative vaccine efficacy (i.e., comparing the modRNA vaccine with the control vaccine) rather than absolute efficacy (i.e., comparing the modRNA vaccine with placebo) as the primary end point. Such a design results in the extrapolation of the efficacy rather than a direct calculation. In addition, as a single-season trial, our ability to show the relative vaccine efficacy against all WHO-recommended influenza strains (A/H3N2, A/H1N1, B/Victoria, and B/Yamagata)[15] was reduced. Although one quarter of the participants in our trial were at risk for severe influenza, the extrapolation of these findings to other populations (children and persons who are immunocompromised, pregnant, or older than 64 years of age), regions, and demographic groups should be done with caution because of the exclusion of these populations from this U.S.-based analysis.

The ability of the modRNA vaccine platform to produce swift and large volumes of efficacious vaccines with acceptable safety was critical during the Covid-19 pandemic but is also important for potential application in the prevention of seasonal respiratory illnesses such as influenza. This randomized trial showed that the modRNA vaccine provided both similar and improved prevention of a first episode of laboratory-confirmed influenza in adults between the ages of 18 and 64 years. This protection was achieved with a vaccine that was designed to encode only the hemagglutinin influenza antigen, but modRNA vaccines could potentially target other influenza virus antigens as well. The modRNA platform offers promise for the development of influenza vaccines and may improve upon existing products.

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